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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,747	08/25/1998	FERNAND NARBEY TOROSSIAN	TORO-0101-PU	8139

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EXAMINER	
SHAHNAN SHAH, KHATOL S	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/125,747	TOROSSIAN, FERNAND NARBEY	
	Examiner	Art Unit	
	Khatol S Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *9-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The request filed on January 16th 2002, paper # 23 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/125,747 is acceptable and a CPA has been established. An action on the CPA follows.

2. Preliminary Amendment received January 16th 2002, paper # 24 is acknowledged. Specification page 13, lines 5-6 was amended. New claims 17-28 were added.

3. Currently claims 9-28 are pending.

Rejection(s) Maintained

4. The rejection of claims 9-16 under 35 USC § 112, First Paragraph made in paragraph 7 of the office action mailed 08/ 28/ 2001 (paper # 23) is maintained.

New Objections

Specification

5. The disclosure is objected to because of the following informalities:

Use of the brackets in the specification could lead to deletion of information within the brackets during the issue and printing processes. Accordingly, the portion of the specification as identified below is required to have the brackets removed before passing the case to issue. See 37 CFR 1.125 and MPEP § 608.01(q). For example the brackets are used in the specification page 1, (lines 8 and 11), page 3 (line 19), page 4 (line 1), page 6 (line 8), page 7 (line 11) and page 16 (lines 15, 19 and 22).

Appropriate corrections are required.

Claim Objections

6. The claims are objected to because of the following informalities:

Claim 17 the species "pylori" is misspelled.

Claims 23 and 24 recite the term " resisting to"; the correct term is "resistant to".

Appropriate corrections are required.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 9-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an immunomodulatory and anti-*Helicobacter*- specific vaccine complex.

The specification fails to set forth sufficient evidence showing that the claimed vaccine complex could be made with "dual molecules" of part (a) of claim 9 comprising any " functional amino acid arm" and any " genetic ribonucleic acid arm". As drafted currently, infinite functional amino acid arms and infinite genetic ribonucleic acid arms are included in the scope of the claim(s), but no guidance has been provided as to their source and as to how they are produced. Furthermore, the immunologic and biologic specificity of these two arms and the precise mechanism by which these unspecified "arms" accomplish the alleged results, i.e., of being effective against "antibiotic resistant bacteria", " recidivations of the initial digestive tract pathology" of unknown etiology, is undisclosed. There is no evidence that subjects of Examples

2-4, who were treated with the complex of the instant invention, were effectively treated against Helicobacter- induced gastritis or duodenal ulcer, because there is no disclosure about the actual etiology of gastritis or duodenal ulcer in these subjects.

Claims 12, 19 and 20 recite the immunomodulatory and vaccine complex of the instant invention for use in the treatment of diseases caused by *Helicobacter* bacteria "by the production of antibodies". However, the specification on page 3, lines 3 and 4, states the "inefficacy" of the *Helicobacter*-specific antibodies in protecting an individual.

The specification does not enable a vaccine comprising the components recited in part (a) of claim 9. Instant specification does not provide a clear written description of "a functional amino acid arm, ensuring binding to a target, with a genetic RNA arm corresponding to the coded description of the composition of the functional arm" (claim 9). Whether or not these components are of bacterial or non-bacterial origin is not disclosed.

Furthermore, page 13 of the specification recites collagen type III as the "immunity adjuvant factor", and the complex as containing "amino acid sequences" of the collagen type III. However, claims 11 and new claim 18 recite that the amino acids from collagen are selected from the various amino acids recited in the claims. The collagen type III is stated on page 13 to be characterized by "Amino acid sequences containing the following concentrations expressed in g/kg" shown on page 13, wherein several individual amino acid residues are recited one below the other. No amino acid sequences are provided or identified specifically by a SEQ ID number. It is unclear what Applicant means by "amino acid sequences" from collagen to the individual amino acids concentrations in g/kg (not sequences) recited on page 13. With this description, one of ordinary skill in the art would not be able to understand whether the whole sequence is

present in the complex, or any one of the recited amino acids is included in the complex, or a mixture of any of these amino acids is included in the complex, and therefore would not be able to make and/or use and/or reproducibly practice the invention without undue experimentation.

Further, the specification does not allow one of ordinary skill in the art to grasp the nature of the association between the multiple components present in the "complex". For example, the optimal amounts or proportions of different "bacterial membrane fractions", i.e., glycopeptides and/or lipopolysaccharides and the ribonucleic acid arm, that should be present in the complex such that the complex can accomplish its alleged therapeutic and/or preventive functions are not disclosed.

The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity for prevention or treatment of *Helicobacter* infection. The art recognized standard for the determination of Helicobacter pylori infection is endoscopy and evaluation of tissue samples for the presence or absence of Helicobacter (see page 661, Buck et al, 1986). Data obtained from challenge experiments must demonstrate an art recognized standard of improvement over the control in order for the composition to be considered as being useful for treatment or prevention of infection and disease. This information is essential for the skilled artisan to be able to use the claimed composition (vaccines) for their intended purpose of a *Helicobacter* vaccine. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced.

The prior art teaches that Helicobacter pylori vaccines are unpredictable, specifically, in the type of effect they will have on preventing or treating infection; the ability to reasonably

predict the capacity of a single bacterial immunogen, to induce protective immunity is problematic. In HP WORLD-WIDE, a publication from Brocades Pharma BV Leiderdorp, The Netherlands, February 1992, data was presented stating that immunization does not appear promising. Parenteral immunization of specific pathogen free mice with *H. felis* gave no protection against gastric colonization; previous oral infection only delayed colonization (page 3 ,Heap, K, Australia). The article also taught that "although intra-peyers patch immunization of killed H. *pylori* in rats shows that the gut mucosa can mount a vigorous immune response, oral immunization with either live or killed bacteria induced no significant serum or salival antibody response (page 3 Dunkley, M, Australia). Blaser also warned that because of the possible autoimmune component of the disease the wrong vaccine could actually make things worse." (see page 3).

Yokota et al (1997) teaches that Helicobacter pylori polysaccharide are of low antigenicity and that while some strains stimulated an immune response *in vivo*, it was strain specific (see abstract and page 3509).

It is known in the art that vaccines convey protection from infection and disease. Rappuoli et al (European Journal of Gastroenterology and Hepatology, 1993, Vol.5, (suppl. 2) pages 576-578) teach that development of a vaccine against *Helicobacter pylori* would involve four major steps:

1) identification of the factors required for virulence;

2) large-scale production and characterization of the virulence factors;

3) development of appropriate animal models to test the virulence and immunogenicity of the molecules identified; and

4) identification of the type of immunity able to prevent infection and disease (see abstract). In the instant specification no art recognized *in vitro* or *in vivo* models are shown in which protection is produced from instantly claimed invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the court of appeals in In re Wands, 8 USPQ 2d 1400 at 1404 (CAFC 1988).

These factors include 1) the quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, and 8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to a vaccine complex having claimed functional feature of capability of generating protective responses, 3) there are no working examples which suggest the desired results of a vaccine against *Helicobacter*, 4) the nature of the invention involved the complex and incompletely understood area of protective immune responses against *Helicobacter*, 5) the state of the prior art shows the lack of correlates to immunity with *Helicobacter*, 6) the relative skill of those in the art is commonly recognized as quite high (post – doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability in the art, and lack of

guidance on how to obtain the desired effect using the claimed vaccine complex it is determined that it would require undue experimentation to make and/or use the claimed invention. In summary, the actual invention is not described in such a way that one skilled in the art could grasp the invention and make and/or use the invention and/or reproducibly practice the invention with a reasonable expectation of success, without undue experimentation. In the absence of specific guidance and evidence, instant claims are viewed as not meeting the enablement provisions of 35 U.S.C. § 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 9-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 17 and all their dependent claims recite the term " immunomodulatory". The term is not defined by the claims or the specification.

Claim 9 is vague and confusing in the recitation of "said ribonucleic acid arm of being of ribosomal origin", because the earlier recitation in the claim is to " a genetic ribonucleic acid arm" pertinent to the dual molecules of part (a) of the claim, and not pertinent to the bacterial membrane fraction of part 9 (b).

Claim 9 is vague and indefinite in the recitation of "a genetic ribonucleic acid arm corresponding to the coded description of the composition of the functional arm", because it is unclear what applicant means by "the coded description". It is not understood which functional

arm applicant is referring to. How does one identify that an "arm" is "functional"? Functional in what sense.

Claim 12 depends from claim 9, the vaccine complex of which comprises dual molecules of unspecified sources and bacterial membrane fractions and ribonucleic acid arm of ribosomal origin from selected species of *Helicobacter*. What is the specificity of the antibodies? Are these antibodies specific to the dual molecules or to the part (b) components?

Claim 18 recites, " wherein the amino acid sequences from collagen comprise amino acids selected from the group consisting of..." It is unclear what Applicant means by "amino acid sequences" from collagen. No amino acid sequences are provided or identified specifically by a SEQ ID number.

Claim 19 depends from claim 17, the vaccine complex of which comprises molecules of amino acid sequences from type III collagen and bacterial membrane fractions and ribonucleic acid extracted from selected species of *Helicobacter*. What is the specificity of the antibodies? Are these antibodies specific to all molecules or to the part (b) and (c) components?

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is (703) 308-8896. The examiner can normally be reached on 7:30 AM - 4 PM from Monday through Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned to is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

4/5/02

Khatol Shahnan-Shah, BS, Pharm, MS

Biotechnology Patent Examiner

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